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Dear Professor Lederberg,

I apologise for being so long in replying to your letter but I have been away on holiday and have only just now returned.

Thank you for your interest in my note in "Nature". The phenomenon of apparent change in phage type was noted in this laboratory almost accidentally and has not been observed with all of our strains.

There are many strains which are penicillin-sensitive and of lysotypes belonging to Grp III, just as there are pen-resistant strains of lysotypes belonging to Gp's I and II. Thus it is not a simple relationship. The penicillin-sensitive Gp. III strains occur fairly frequently among the general population of this area - say 15% of carrier strains, but they are not the same types as the Gp.III strains which I find in hospital or obtain after exposure of sensitive strains to penicillin.

However, one great difficulty in the interpretation of bacteriophage typing of Staphylococci, is that since the reactions with Gp.III phage are not well defined it is sometimes difficult to decide whether or not a strain is different from another on the basis of minor, or even a major difference in the phagelytic pattern. For a time, when studying the antibiotic-resistant strains ~~of~~ from a single hospital, I was of the opinion that there was some sort of "gradation" of pattern with differing antibiotic sensitivity, e.g. :

	Type
Penicillin resistant Streptomycin sensitive	47/54/75
Penicillin resistant Streptomycin resistant	47/75/76/77
Penicillin resistant Streptomycin resistant Tetracycline resistant	Not typable or weak reactions to 76/77

but/

but experimental work has not given support to the view that these differences in phage pattern could be acquired alone with the acquisition of resistance to ~~sensitive~~ successive antibiotics.

On the whole I would agree with you that exposure to the drug appears to be a condition for the change in phage type and this is further supported by the following evidence (which may also fit with the "prophage" theory).

We occasionally observe spontaneous ~~autol~~phage lysis in strains of Staphylococci isolated from cases. This phenomenon occurs with greater frequency when the strains are exposed to penicillin of a certain concentration, as occurs when we are carrying out initial antibiotic-sensitivity determinations. If the phage released at this phase is separated from the parent culture it is usually found to be of Gp.III, and also similar to phages which now lyse the penicillin-resistant variants.

Thus,

original culture say of type 3A, resistant to phage 77	Exposed to Penicillin. Autolysogenesis Phage separated and found to be similar to Phage 77	Penicillin-resistant variant isolated not auto-lysogenic. type 77, resistant to phage 3A.

The problem warrants much closer looking into, and this we are doing.

I have attempted to induce the resistance of Staphylococci to bacteriophage and correlated this with change in sensitivity to antibiotics, but so far without clear-cut results. I have also carried out experiments with antibiotic-sensitive and resistant strains isolated from the same environment to see whether cross-resistance and cross-changes in phage type could be induced, and also if there was any significant difference between the two parent strains in these respects. The only satisfactory evidence so far is in support of the common finding that penicillin resistant Staphylococci (i.e. penicillinase producers) are frequently resistant to other antibiotics but penicillin-sensitive strains are not (under natural conditions). Unfortunately, penicillinase production is not a monopoly of Gp. III lysotypes but does occur with Gp. I and II.

I/

I shall study your most helpful suggestions on replica plating and indirect selection. It would indeed be interesting to see if spontaneous mutants, resistant to antibiotics, retained their lysotype.

I enclose a copy of the note in Nature and some others which are only indirectly concerned, but may possibly be of interest to you. Most of my work on this problem has not yet been published.

Yours sincerely,

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